COAGULATION TIME OF BLOOD SPECIMENS FROM TUBERCULOUS PATIENTS.

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Is there a relation between the tendency to hemoptysis which is exhibited by certain patients having pulmonary tuberculosis and the coagulation time of the blood? The answer to this question was the object of the investigation here recorded.

Hemoptysis, or bloody sputum, is understood to mean pure or nearly pure blood in considerable quantity, a teaspoonful or more, and not merely streaks of blood such as may come from an irritated throat.[1]

Some tuberculous patients and, according to Fishberg, a large proportion of cases of phthisis, pursue their course and terminate in recovery, or fatally, without any hemoptysis. Fishberg found a wide variation in the statistics concerning the frequency of this symptom during the course of phthisis, some reports stating 25 and others 80 per cent., with many figures intermediate.[2]

Other patients seem quite predisposed to hemoptysis and are characteristically known as "hemorrhage patients."

Our experiments were made during a period of six months, thus allowing for any possible seasonal influence, and also for the opportunity of selecting typical cases from the 300 patients treated in that interval at the North Reading State Sanatorium. Hemoglobin percentage was estimated in each case by the Dare instrument.

The coagulation time of the blood of each patient is used only on a comparative basis in these experiments. One must not expect to contrast the figures themselves with those obtained by another method. Cannon and Mendenhall[3] point out clearly that there is no definite coagulation time quite independent of the method used because the conditions peculiar to any coagulometer are likely to affect the time of clotting.

A consideration of the various methods which have been used in estimating blood coagulation time and their relative merits seem hardly necessary here. Addis reviewed this matter.[4] Cannon and

[1] Cabot, Richard C.: Physical Diagnosis, 1910, p. 325.

[2] Fishberg, Maurice: Pulmonary Tuberculosis, 1916, p. 186.

[3] Factors Affecting the Coagulation Time of Blood, Am. Jour. Physiol., 1911, xxiv, 225.

[4] Addis, T.: Coagulation Time of Blood, Quart. Jour. Exper. Physiol., 1908, i, 305.

Mendenhall[5] added still another method, based upon the principles laid down by Addis, and after they had gone over the work done by Addis and by Morawitz[6] on the various coagulometers.

We therefore were fortunate in being able to adopt Cannon's method, in which he eliminated the objectionable features mentioned in the criticisms by the foregoing authors in their discussion of the various coagulometers.

In the first place it is best to define the principles stated by Addis and approved by Cannon under which work of this sort must be carried on:[7]

1. The blood must always be obtained under the same conditions.
2. The estimates must all be made at the same temperature.
3. The blood must always come in contact with the same amount and kind of foreign material.
4. The end-point must be clear and definite and must always indicate the same degree of coagulation.

In addition to these four conditions, Cannon decided that the ideal instrument should yield a permanent objective record made by the blood itself.[8]

Our coagulometer was designed after the pattern of Cannon's but was somewhat modified in construction and working arrangement because the factors in our problem differed.

A brief description of the instrument used is as follows:

APPARATUS. The upright with attached balance beam of a prescription scales was set up on a small wooden stand. This platform rested on four leveling screws, which could be so adjusted as to bring the upright perpendicular, thus insuring proper equilibrium for the balance.

One arm of the balance beam was prevented from rising above a horizontal position by a check, a small brass lever operating at right angles to the beam, secured to a wooden upright. This check could be raised and lowered with a slight touch of the finger. At the opposite end of the beam was a ring to which could be easily hooked a short length of copper wire. This wire, 7 cm. long and 0.6 mm. in diameter (gauge 21 B. and S.) was bent above into a hook and below into a small ring slightly less than 2 mm. in diameter. The small ring would then rest in the cannula containing the blood in such a way as to allow for a descent of the wire through the blood to about 5.5 mm.

Eight of these wires were made up as nearly standard as possible, for when hung on the beam the weight of the wire, allowing for a counter-balance at the other end of the beam, made this end of the beam 60 mgm. the heavier.

The cannulas were fairly uniform in size and in capacity in accord-

[5] Loc. cit.
[6] Loc. cit., quoted by Cannon and Mendenhall, p. 225.
[7] Addis, T.: Loc. cit.
[8] Loc. cit., Cannon and Mendenhall, p. 226.

ance with Cannon's careful directions that all dimensions should be as nearly standard as possible, so that the amount of blood[9] received in them should be fairly constant and that the wire hanging in the blood should present approximately the same surface in different observations.

SIZE OF CANNULAS.

Outside diameter	3.5 mm.
Inside diameter	2.0 mm.
Length over all	23.0 mm.

The cannula rested nearly submerged in a water-bath at 25° C. A rubber collar held the cannula from entirely slipping through the hole in the bracket. The bracket was accurately adjusted to allow for free descent of the wire and also for the proper submersion of the cannula in the water-bath. A small circulation coil warmed by an alcohol lamp kept the water-bath at uniform temperature. Addis[10] insists upon the strict necessity of carefully fulfilling this condition of constant temperature.

An electromagnetic signal which rang at half-minute intervals completed the outfit.

Drawing the Blood. The blood was taken from the lobe of the ear, which was previously cleansed with soap and water, alcohol, and ether. The cannulas were cleaned in running cold water, then passed through ether in order to destroy all traces of fibrin ferment such as might remain from a former case.

The ear lobe was punctured with the point of a sharp bistoury and the time then noted. This knife was cleaned with ether and alcohol after each operation. Immediately as the blood drop appeared the tip of the cannula was applied to the drop. Blood quickly flowed into the cannula to within about 2 mm. of the rubber collar.

The tip of the cannula was then sealed with plastiline, the cannula set in the bracket in the water-bath, the wire hung on the balance beam and inserted in the cannula.

The small ring would then be immersed in the blood. A thin coating of liquid petrolatum, previously applied to the upper third of the inside of the cannula, served two purposes. The oil covered the surface of the blood, thus preventing contact with the air and also lubricated the unfilled bore of the cannula so that the wire would not stick to the side. Therefore the wire, in falling into the blood at regular intervals represented the same weight each time. In about thirty seconds from the time the ear was punctured the cannula had been filled and placed in the water-bath, and all was in readiness for operation of the apparatus.

Operation of Apparatus. This operation consisted of raising the check with the finger at every half-minute record of the signal. The other end of the beam, heavier by 60 mgm. would fall, allowing

[9] Loc. cit., p. 227.

[10] Loc. cit., p. 331.

the wire to sink into the blood. The check would then be lowered, causing the wire to rise and the beam to assume its usual horizontal position.

So long as the wire sank through the blood to the full extent of the 5.5 mm. play there was evidence that the blood was still fluid and that coagulation had not taken place.

END-POINTS. As soon as the blood clotted the weight of 60 mgm. was supported and the balance beam failed to move through its usual excursion. This phenomenon usually appeared suddenly—that is, the twelfth descent of the wire, for instance, would be unobstructed and as free as preceding movements; then at the next half-minute record the downward movement would be jerky and slow. The subsequent movement thirty seconds later would be interfered with and blocked; this recorded the end-point and testified to a sudden crisis of coagulation, which was confirmed by the jelly-like clot revealed on the wire ring and in the cannula when these were removed from the apparatus.

The coagulation time of a particular specimen of blood was measured by that interval elapsing between the time of puncturing the skin and the time when the end-point just described occurred.

RESULTS. One hundred and forty-eight specimens of blood were put through the apparatus for the determination of coagulation time. Sixteen of these trials produced variable results because the blood was obtained under dissimilar conditions—that is, the specimen in each case was taken from the needle of a syringe used in drawing a quantity of blood from the arm vein. The variable factors in this method of collection precluded the probability of approximately constant results in this group, and accordingly these 16 cases were thrown out.

Of the 132 remaining cases 12 represented second trials on the same patients. Therefore 120 different patients were considered.

Of the total 132, 65 gave a history of hemoptysis and 63 could not recollect this symptom.

Of the tuberculous, 47 were classed as closed and 73 as open cases, the former group including those without symptoms and with local signs practically quiescent, while the latter group represented patients showing one or another of the signs and symptoms of pulmonary tuberculosis.

The average coagulation time in 130 trials was seven minutes forty-five seconds. Two patients with open, semi-active pulmonary tuberculosis yielded specimens which did not coagulate within twenty-eight and thirty-four minutes respectively, and no end-points were observed. Each case was observed to have had recent hemoptysis. Four months later, after some improvement and no recurrent hemoptysis, one of these men presented a blood specimen which coagulated in six minutes. The other patient had left the institution in the meantime and no second specimen was available.

With the exception of these 2 cases the extreme increased coagulation time was twenty minutes forty-nine seconds recorded in 1 case. Between fifteen and twenty minutes only 1 case was recorded. These two men had no history of hemoptysis.

In the accompanying table the cases other than those above are grouped according to their recorded coagulation time:

Minutes.	Total.	Open cases.	Closed cases.	Cases probably non-tuberculous.	Cases with hemoptysis.	Cases without hemoptysis
15 to 14 . .	2	2	..	..	1	1
14 to 13 . .	3	2	1	..	2	1
13 to 12 . .	4	1	2	1	2	2
12 to 11 . .	6	4	2	..	3	3
11 to 10 . .	7	3	4	..	5	2
10 to 9 . .	16	14	2	..	8	8
9 to 8 . .	13	12	1	..	7	6
8 to 7 . .	15	8	7	..	9	6
7 to 6 . .	31	16	11	4	16	15
6 to 5 . .	14	3	10	1	6	8
5 to 4 . .	16	7	7	2	6	10
4 to 3 . .						
3 to 2 . .	1	1	..	..	..	1

A study of the data thus arranged discloses no gross evidence one way or the other of any relationship between the coagulation time of the blood and the tendeney to hemoptysis.

SUBSTUDY. The history of hemoptysis was more or less remote in some of the 65 patients classed in this group. Accordingly, we selected 13 patients whom we had recently observed having had hemoptysis and determined the coagulation time of the blood in each case. The estimates were:

11 minutes	30 seconds
10 "	
9 "	40 "
9 "	30 "
9 "	30 "
9 "	30 "
9 "	
8 "	30 "
6 "	30 "
6 "	30 "
6 "	30 "
6 "	
5 "	30 "

The first five records referred to patients who were having recurrent pulmonary hemorrhages, although not in any large quantities. The last record, five minutes thirty seconds, referred to a patient who daily expectorated from one to four ounces of blood.

This patient[11] has a history suggesting the aspiration of foreign bodies, probably one or more shoe-nails, and the physical signs

[11] Case No. 2272, North Reading State Sanatorium Clinical Records.

point to bronchial stenosis probably due to foreign body in the bronchus. His sputum is negative for tubercle bacilli and his daily hemoptysis for months is altogether too extraordinary to be explained as merely a symptom of pulmonary tuberculosis. Eliminating this case from the group the average time is eight minutes thirty seconds.

We then selected 12 non-hemoptysic patients, in each of whom the disease process could be assumed to parallel those of the first group. The records of coagulation time obtained were:

	10 minutes	30 seconds
	10 "	
	9 "	30 "
	9 "	30 "
	9 "	30 "
	9 "	
	8 "	
	8 "	30 "
	7 "	30 "
	7 "	
	6 "	30 "
	6 "	30 "
Average	8 "	30 "

Each case of the twenty-four in this substudy was one of advanced pulmonary tuberculosis with positive sputum.

As a matter of observation it seems that those patients far advanced in the disease and with active signs and symptoms have increased coagulation times. On the other hand, we obtained a record of six minutes thirty seconds, for instance, in a specimen from a patient who was a bed case with far-advanced disease.

In relation to this and other similar variations found in our results we must respect the warning which Addis sounds. He believes that the indirect method of determining blood-coagulation time will probably give untrustworthy results in pathological condition, due to the fact that the agglutination of the blood is increased in disease[12]—that is, the corpuscles may be agglutinated by their own serum, and thus agglutination may closely simulate coagulation.

Our coagulometer operates as an indirect method because the evidence that coagulation has occurred is deduced from the change in the physical character of the blood—that is, a loss of fluidity. Addis contrasts this method with the direct in which the end-point of coagulability is determined by the first appearance of fibrin.

Cannon's apparatus represents a combination of direct and indirect methods. The wire used in their experiments was counter-balanced at 30 mgm. while ours was at 60 mgm. We therefore doubled the weight to be supported by the coagulated blood when the end-point had occurred, and our reason for doing so arose from Addis's objection.

[12] Addis: Loc. cit., p. 320.

It appears possible that even with using the heavier wire we encountered this obstacle of agglutination. All the necessary conditions were complied with carefully in order to ensure approximately constant results, and yet it must be admitted that the results shown are so variable as to invite serious criticism. We doubt if experimental error could be the entire basis of such criticism.

EXPLANATORY NOTES. We preferred the ear rather than the finger as a source from which to obtain the blood. In tuberculous patients the ears invariably yielded the specimen promptly, while the fingers, more or less subject to chronic passive congestion, were not so satisfactory in this respect. Addis found that blood differed very little, if any, in time of coagulation whether it was drawn from a deep or superficial source,[13] and that increased congestion, as would be produced by cleansing the ear lobe, made no difference.[14]

Addis found no diurnal variation in the coagulability of blood, the coagulation time of the blood of the same individual being constant at different times of the day and even on different days.

Addis used the first drop of blood to appear.[15] Cannon and Mendenhall found that the first few samples of blood taken from an animal showed rapid or somewhat irregular rates of clotting.[16]

In applying their method to testing human blood they found on one occasion that the first sample showed the largest variation in coagulation time from the average—that is, +0.6 minute, while the second and fifth samples showed the least—that is +0.1 minute. The average error was +0.3 minute.[17]

The samples of blood which we used in our experiments composed the first few drops drawn, and this blood was quickly introduced into the cannula within a few seconds of the time when it first appeared.

Special care was necessary in this operation to prevent any longer contact of the blood with the air. Moreover, no specimen was taken up from skin previously covered with recently shed blood. Addis[18] has shown conclusively the large experimental error arising from neglect of complying with this condition.

The puncture made in each case was sufficient to ensure the prompt appearance of the blood drop and also an approximately constant rate of outflow.

In drawing a quantity of blood from a vein into a test-tube for serological examination we have occasionally observed a much increased coagulation time in certain specimens. While this is an inaccurate method of determining coagulability, due to varia-

[13] Addis: Loc. cit., p. 330.
[14] Loc. cit.
[15] Addis: Loc. cit., p. 315.
[16] Cannon and Mendenhall: Loc. cit., p. 231.
[17] Ibid.
[18] Addis: Loc. cit., p. 315.

tions in temperature and in conditions influencing the contact of the blood with foreign surfaces, yet the difference in clotting times have often been extraordinary.

Upon examining later the contents of such tubes we have found in some a clotted mass of serum, "chicken-fat" clots, of tough, white, fibrous consistency. These specimens were common to pathological cases with advanced disease. Whether or not the formation of this so-called "serum clot" may have a bearing upon the agglutinative process simulating blood coagulation we leave to conjecture.

SUMMARY. 1. One hundred and twenty patients yielded one hundred and thirty-two specimens of blood for the estimation of coagulation time. Of these patients 8 were probably non-tuberculous. The rest were afflicted with pulmonary tuberculosis, 73 being open and 47 closed cases. Of the 120 patients 54 per cent. gave histories of hemoptysis.

2. The average clotting time was seven minutes forty-five seconds.

3. Grouping these cases in tabular form according to:

(*a*) Coagulation time,

(*b*) Occurrence or non-occurrence of hemoptysis, and

(*c*) Stage of disease activity or quiescence, we find no striking demonstration of results.

4. A substudy of 24 cases was made. Twelve patients with recent hemoptysis showed coagulation times increased in several instances and in average time eight minutes thirty seconds. Twelve patients without hemoptysis and with disease processes parallel to those of the patients in the first group showed coagulation times increased in as many instances as among those of the first group. Average was the same, eight minutes thirty seconds.

5. The indirect method of determining blood coagulation time may produce variable results when applied to pathological conditions.

6. No attempt was made to show the results of medication with calcium salts. Addis found that the coagulation time[19] of the blood was unaffected by the administration by month of soluble calcium salts. In a notable study[20] Addis found that the amount of ionizable calcium in the blood is increased by giving soluble calcium salts by mouth but the increase which is brought about is considerably less than is necessary before any appreciable effect is produced on the coagulation time.

[19] Addis: Loc. cit., p. 332.

[20] Addis, T.: Quart. Jour. Exper. Med., January, 1909, ii, 163.